ORIGINAL ARTICLE

The International Association for the Study of Lung Cancer Thymic Tumors Staging Project: The Impact of the Eighth Edition of the Union for International Cancer Control and American Joint Committee on Cancer TNM Stage Classification of Thymic Tumors

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ABSTRACT

Objectives: The International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee-Thymic Domain conducted a web-based cross-sectional survey to assess the acceptance of the TNM thymic staging system in the thoracic community.

Methods: A 50-item, web-based questionnaire was circulated among the members of the major thymic organizations worldwide from September to December 2018. The survey consisted of six sections (general information; overall perception of the TNM system; pretreatment staging; T category; N category; and perioperative treatments).

Results: In total, 217 responses were collected from 37 countries in four continents. The TNM classification was considered useful by 78% of the responders (N = 169); the Masaoka-Koga staging system was being used by 87% of the responders (N = 189). With regard to the T category, most responders (mostly surgeons) felt that the capsular and mediastinal pleural involvements should be considered separate T categories. As for the N category, 48% of the responders (N = 105) used the International Thymic Malignancies Interest Group/International Association for the Study of Lung Cancer thymic nodal map, and lymph node dissection (N1/N2) was performed for 50%/21% thymomas and 66%/41% thymic carcinomas. While analyzing the results by the three continents (Europe, Asia, and Americas), responders in Asia were found to report the largest use of the TNM system, the greatest attention to the N category, and the best participation in international thymic databases.

Conclusions: The survey indicates that the Union for International Cancer Control/American Joint Committee on Cancer TNM stage classification of thymic tumors is gaining acceptance among the scientific community. The present results will guide the work of the Staging and Prognostic Factors Committee-Thymic Domain for the revision of the ninth edition of the TNM stage classification of thymic tumors.

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Keywords: Survey; Thymoma; Thymic carcinoma; Thymic tumors; TNM

Introduction

The TNM system of classification of neoplasms is a globally accepted system that defines the anatomical extent of the tumor. Owing to its importance, the TNM stage classification of all human solid organ tumors is under the supervision of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) that are responsible for the release and the revisions of the TNM.

The International Association for the Study of Lung Cancer (IASLC) initiated a data-based project for the TNM stage classification of lung cancer. Subsequently, UICC and AJCC gave IASLC the mandate to lead the development and revisions of the stage classification initially for lung cancer and subsequently for other thoracic malignancies. The IASLC Staging Project is managed by the IASLC Staging and Prognostic Factors Committee (SPFC). The SPFC is structured into four domains: lung cancer, mesothelioma, thymic tumors, and esophageal cancer. The previous revision (eighth edition) of the TNM stage classification of thoracic malignancies became effective in 2018 in the United States and in 2017 in the rest of the world. For the first time, a data-based TNM-based stage classification was proposed for thymic tumors,[1-3] replacing the Masaoka (M) and Masaoka-Koga (MK) systems,[4,5] which have been the most employed thymic tumor staging systems for more than 35 years.

Although the UICC/AJCC TNM system for thymic tumors has maintained some concepts from the MK system, there are a number of important differences, including a nodal classification according to the International Thymic Malignancies Interest Group (ITMIG)/IASLC thymic nodal map, the consolidation of all tumors invading up to the mediastinal pleura into TNM stage I, and the importance of direct pericardial invasion (stage II). All these modifications represent a major change in the approach to thymic tumors, which will presumably take time to be incorporated into clinical practice.

For this reason, the IASLC SPFC-Thymic Domain (TD) designed and circulated a web-based survey inviting members of all the major thymic organizations to explore the actual applicability, perceived utility, and limitations of the new stage classification. The aim of the present report is to describe and discuss the results of this survey.

Materials and Methods

A web-based, online questionnaire was designed by the IASLC SPFC-TD. An initial draft was circulated among all members of the SPFC-TD, including surgeons,

pathologists, radiation and medical oncologists, and radiologists, and the final version was discussed and agreed on.

The survey was sent to the following thymic organizations: European Society of Thoracic Surgeons (ESTS), Korean Association for Research on the Thymus (KART), The Chinese Alliance on Research in Thymomas (ChART), the Réseau Tumeurs Thymiques et Cancer (RYTHMIC), and the Japanese Association for Research in the Thymus (JART). In addition, a blast e-mail was sent to the IASLC members. The questionnaire was sent in September 2018, and the members were invited to respond by December 31, 2018. Three reminders were sent during this period.

The final questionnaire consisted of 50 questions structured into six sections (Appendix E). Section 1 included general information of the responding center; section 2 included questions about the overall perception of the utility and the practical use of the UICC/AJCC TNM staging system for thymic tumors; section 3 dealt with the pretreatment staging (cTNM), particularly on the perceived applicability of imaging, specifically thoracic computed tomography (CT), positron emission tomography (PET)-CT, and chest magnetic resonance imaging (MRI) in the clinical stage; sections 4 and 5 included questions about the T and N categories; and the last section investigated the use of perioperative therapies (chemotherapy and/or radiotherapy) according to the new TNM stages.

Data are presented as numbers and percentages (rounded to one decimal). Comparison among percentages was performed using the chi-square (Fisher's exact test when appropriate). A p value less than 0.05 was regarded as significant.

Results

Overall, a total of 217 responses were collected.

Sections 1 and 2: Center Information and General Feedback of the TNM Classification

The responders were from 37 countries and four continents. The largest contribution was from Europe (N = 87), followed by Asia (N = 84), Americas (N = 36), and Africa (N = 10). When analyzed by countries, the largest contribution was from People's republic of China (N = 49), followed by Italy (N = 25), the United States (N = 19), and France (N = 16) (Appendix F; Table 1).

Seventy-one percent (N = 154) of the responders were surgeons, although there was representation from other specialties. More than 90% of the responders indicated that they treated more than five cases per year and 64% treated more than 10 cases per year; 88% of the responders employed minimally invasive techniques (video-assisted thoracoscopic surgery-VATS/Robotic-assisted thoracic surgery-RATS) for the surgical treatment of thymic tumors.

Some specific questions addressed the issue of the awareness, availability, and current use of the eighth edition of the UICC/AJCC TNM stage classification compared with that of the MK system. Overall, there was high awareness of the new staging system (N = 204, 94%), and the availability of material illustrating the stage classification in the literature/web was perceived as "good" (N = 141, 65% found it good or very good). In addition, 78% responders (N = 169) indicated that they found the TNM classification useful and 50% (N = 98) considered it user friendly. The TNM stage classification of thymic tumors was used in daily clinical practice by 64% of the responders (N = 138), whereas the MK system was used at the same time by 87% of the responders (N = 189). Both the systems were used on the basis of imaging to assess resectability (53% MK and 40% TNM).

Section 3: Pretreatment Staging

CT was used by most responders as the accepted standard for clinical staging (96%, N = 209) (Table 2). The second most employed imaging technique was fludeoxyglucose PET-CT (N = 101, 46%), most often in combination with CT or chest MRI. Chest MRI was employed in approximately one-third of the cases (33%, N = 72), usually in association with CT of PET-CT for advanced disease. In addition, the survey investigated the perceived usefulness of either CT or chest MRI in the clinical staging of different T, N, and M categories. CT was perceived to be effective in clinically staging cT1a (61%), cT3 (63%), cT4 (60%), cM1a (72%), and cM1b (77%) and only moderately effective in cT1b (41%), cT2 (39%), cN1 (43%), and cN2 (47%). Chest MRI was indicated as effective in clinically staging cT1a (60%), cT1b (56%), cT2 (59%), cT3 (70%), and cT4 (73%) and less effective in cN1 (25%), cN2 (27%), cM1a (43%), and cM1b (29%).

Section 4: T Category

Most responders (N = 180, 83%) indicated that they routinely marked the surgical specimen. Capsular, mediastinal pleural, and direct pericardial involvements were considered important aspects of the T category, as confirmed by 79% (N = 171), 80% (N = 174), and 90% of the responders (N = 200), respectively. Seventy-two percent (N = 157) and 60% of the responders (mostly surgeons) (N = 130) believed that operation played a role in advanced diseases including clinical stage IVA (pleural/pericardial nodules) and IVB (N2 disease), respectively (Table 3).

Table 1. Center/Responder's Information and General Feedback of the Union for International Cancer Control/American Joint Committee on Cancer TNM Thymic Stage Classification and Masaoka-Koga Thymic Staging System (N = 217)

Question	No.	%
Continent	—	—
Africa	10	5%
Americas	36	16.5%
North	25	—
Central	2	—
South	9	—
Asia	84	39%
Europe	87	40%
Specialty	—	—
Diagnostic radiology	7	3%
Medical oncology	15	7%
Radiation oncology	17	8%
Pathology	13	6%
Pulmonology	9	4%
Surgery	154	71%
Other	2	1%
Volume activity (y)	—	—
<5	20	9%
5-10	58	27%
10-20	61	28%
20-30	26	12%
>30	52	24%
Type of surgical approach	—	—
Video-assisted thoracoscopic surgery/RATS	190	88%
Only open procedures	19	9%
N/A	8	3%
Participation in International databases	—	—
Yes	120	55%
No	97	45%
Awareness of the eighth edition TNM classification of thymic tumors	—	—
Yes	204	94%
No	8	4%
N/A	5	2%
Availability to find information about the TNM in the literature/web (1 = insufficient; 5 = optimal)	—	—
1	12	5%
2	25	11%
3	66	30%
4	75	35%
5	39	18%
Do you currently use the eighth edition of the UICC/AJCC TNM classification of thymic tumors?	—	—
Yes	138	64%
No	74	34%
N/A	5	2%
Do you still use the Masaoka-Koga staging classification?	—	—
Yes	189	87%
No	26	12%
N/A	2	1%
Usefulness of the eighth edition of the UICC/AJCC TNM classification of thymic tumors	—	—
Extremely useful	24	11%
Reasonably useful	88	41%
Useful	57	26%
Little useful	26	12%
Not useful	7	3%
N/A	15	7%
User friendliness of the eighth edition of the UICC/AJCC TNM classification of thymic tumors (1: very difficult to use; 5: extremely easy to use)	—	—
1	7	3%
2	24	11%
3	78	36%
4	81	37%
5	27	12%
Which staging classification do you use to assess resectability?	—	—
Eighth edition TNM classification	86	40%
Masaoka-Koga staging classification	115	53%
N/A	16	7%

RATS, Robotic-assisted Thoracic Surgery; N/A, not applicable; UTCC/AJCC, Union for International Cancer Control/American Joint Committee on Cancer.

Section 5: N Category

The awareness, the current use, and the perceived efficacy of the ITMIG/IASLC nodal map were explored.[2] One hundred fifty-five responders (72%) were aware of a dedicated thymic nodal map, although only 48% responders (N = 105) were using it in their clinical practice and only 54% (N = 117) found it effective (Table 4).

Lymph node dissection of the N1 stations according to the ITMIG/IASLC nodal map was performed in 50% of thymomas (N = 107) and in 66% of thymic carcinomas (N = 144). Lymph node dissection of the N2 stations was performed in 21% of thymomas (N = 45) and 41% of thymic carcinomas (N = 88). Lymph node dissection was performed most often for the T3 category (33%, N = 72) versus the T2 (9%, N = 20) and T1 categories (8%, N = 18). The most frequently resected N1 lymph node stations were the perithymic (N = 160), prevascular (IASLC level #3, N = 127), and para-aortic nodes (IASLC level #6, N = 93). The most frequently resected N2 lymph node stations were the paratracheal (upper paratracheal [IASLC level #2, N = 93] and lower paratracheal [IASLC level #4, N = 102]), subaortic and/or aortopulmonary window (IASLC level #6, N = 103), and internal mammary (N = 71) nodes. When exploring the occasions on which N2 stations were removed, the most frequent occasions were in the presence of a preoperative PET uptake (40%, N = 87),

Table 2. Pretreatment (Clinical) Staging (N = 217)

Question	No.	%
Imaging technique in assessing clinical stage	–	–
CT only	83	38%
MRI only	3	1%
FDG PET-CT scan only	4	2%
CT and FDG PET-CT scan	57	26%
CT and MRI	30	14%
MRI and FDG PET-CT	1	0.5%
CT, MRI, and FDG PET-CT	39	18%
Is CT useful in clinically staging the following categories:	–	–
cT1a	132	61%
cT1b	89	41%
cT2	84	39%
cT3	137	63%
cT4	131	60%
cN1	94	43%
cN2	102	47%
cM1a	156	72%
cM1b	168	77%
Is MRI useful in clinically staging the following categories:	–	–
cT1a	130	60%
cT1b	121	56%
cT2	128	59%
cT3	152	70%
cT4	159	73%
cN1	55	25%
cN2	59	27%
cM1a	93	43%
cM1b	64	29%

CT, computed tomography; FDG PET-CT, fludeoxyglucose positron emission tomography-computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography.

Table 3. T Category (N = 217)

Question	No.	%
Marking of the surgical specimen	–	–
Yes	180	83%
No	25	11%
N/A	12	5%
Should the capsular involvement be included as separate T category?	–	–
Yes	171	79%
No	33	15%
N/A	13	6%
Should mediastinal pleural involvement be included as a separate T category?	–	–
Yes	174	80%
No	24	11%
N/A	19	9%
Should direct pericardial involvement be included as a separate T category?	–	–
Yes	200	92%
No	6	3%
N/A	11	5%
In clinical stage IVA (according to the eighth edition of the UICC/AJCC TNM staging classification of thymic tumors), do you think that operation of the primary tumor + pleural/pericardial implants is appropriate?	–	–
Yes	157	72%
No	24	11%
N/A	36	17%
In clinical stage IVB tumors (N2 disease according to the eighth edition of the UICC/AJCC TNM staging classification of thymic tumors), do you think that operation of the primary tumor is appropriate?	–	–
Yes	130	60%
No	41	19%
N/A	46	20%

N/A, Not applicable; UICC/AJCC, Union for International Cancer Control/American Joint Committee on Cancer.

suspicious intraoperative node(s) (42%, N = 91), and enlarged (>1 cm) preoperative lymph node on CT scan (30%, N = 65) and routinely in thymic carcinomas/Neuroendocrine Thymic Tumors(NETT) (30%, N = 65) and in all advanced thymomas (25%, N = 54). Finally, half of the responders declared that they performed N1 lymph node dissection during minimally invasive procedures, whereas N2 dissection was rarely performed (21% of the responders).

Section 6: Perioperative Treatments

The responders were asked about their opinion regarding the efficacy and level of evidence of postoperative radiotherapy (PORT) in completely resected (R0) thymic tumors and in N+ disease. The reported evidence of efficacy of PORT in R0 T1, T2, and T3 thymomas and thymic carcinomas was 9% (N = 19), 30% (N = 65), and 69% for thymomas (N = 149) and 33% (N = 72), 59% (N = 128), and 78% for thymic carcinomas (N = 170), respectively. The perceived level of evidence for PORT in R0 T1 to T3 for thymomas and thymic carcinomas was "strong" (four out of five categories) according to only 11% of the responders (N = 25) for thymomas versus 30% of responders (N = 65) for thymic carcinomas. For N+ disease, 67% of the responders (N = 146) indicated that they felt that PORT was indicated (Table 5).

More than half of the responders (53%, N = 114) agreed that preoperative chemotherapy was not indicated in potentially resectable stage III tumors; however, postoperative chemotherapy was deemed to be indicated in incomplete resections (R+), N+ complete resections, and never by 30% (N = 66), 41% (N = 89), and 11% of the responders (N = 25), respectively.

Analysis by Continent

We analyzed replies to some questions according to three continents, Europe (N = 87 responders), Asia (including Israel and Turkey; N = 84 responders), and the

Table 4. N Category (N = 217)

Question	No.	%
Awareness of the IASLC/ITMIG thymic nodal map	—	—
Yes	155	71%
No	46	21%
N/A	16	7%
Use in the clinical practice	—	—
Yes	105	48%
No	71	33%
N/A	41	19%
Do you agree with the IASLC/ITMIG thymic nodal map?	—	—
Fully agree	15	7%
Agree	102	47%
Neutral	31	14%
Disagree	12	5%
Fully disagree	7	3%
N/A: I do not know	50	23%
Systematic lymph node dissection of N1 stations thymomas	—	—
Yes	107	50%
No	76	35%
N/A	34	16%
Systematic lymph node dissection of N1 stations in thymic carcinomas	—	—
Yes	144	66%
No	37	17%
N/A	36	17%
Which of the following N1 stations do you remove?	—	—
Low anterior cervical (IASLC level #1)	68	
Perithymic	160	
Para-aortic (IASLC level #6)	93	
Prevascular (IASLC level #3)	127	
Supradiaphragmatic/inferior phrenic/ pericardial	35	
Which of the following N2 stations do you remove?	—	—
Cervical (lower jugular)	47	
Supraclavicular	26	
Internal mammary	71	
Upper paratracheal (IASLC level #2)	93	
Lower paratracheal (IASLC level #4)	102	
Subaortic/aortopulmonary (IASLC level #5)	103	
Subcarinal (IASLC level #7)	56	
Hilar IASLC level 10)	53	
Systematic lymph node dissection of N2 stations in thymomas	—	—
Yes	45	21%
No	131	60%
N/A	41	19%
Systematic lymph node dissection of N2 stations in thymic carcinomas	—	—
Yes	88	41%
No	91	42%
N/A	38	17%
Do you perform systematic lymphadenectomy in the following T categories (irrespective of tumor histologic diagnosis):	—	—
T1 (up to the mediastinal pleural included)	18	8%
T2 (pericardium)	20	9%
T3 (mediastinal structures: potentially resectable)	72	33%
T4 (mediastinal structures: usually unresectable)	14	6%
N/A	93	43%
38. On which occasion do you remove the deep mediastinal/cervical nodes (N2)? (Tick all that apply)	—	—
Routinely	16	7%
In all advanced tumors	59	27%
In advanced thymomas	54	25%
In thymic carcinomas (and NETT)	65	30%
When the lymph node is >1 cm on preop CT scan staging	65	30%
If the lymph node exhibits uptake on preop PET-CT staging	87	40%
When the lymph node seems suspicious during operation	91	42%
Never	1	<1%
N/A	39	18%
39. Do you perform systematic node dissection during minimally invasive (video-assisted thoracoscopic surgery/RATS) resection of thymic tumors in your institution?	—	—
Only N1 nodes	65	30%
N1 + N2 nodes	46	21%
Never: I rely on the nodes that are taken out with the specimen	40	18%
N/A	66	30%

N/A, Not applicable; CT, computed tomography; IASLC, International Association for the Study of Lung Cancer; ITMIG, International Thymic Malignancies Interest Group; NETT, Neuroendocrine Thymic Tumors; PET-CT, positron emission tomography-computed tomography; RATS, Robotic-assisted thoracic surgery.

Americas (North, Central, and South; N = 36 responders). We did not consider the replies from Africa, because of the small number of responders (N = 10) (Table 6).

The type of surgical access, the participation in international databases, and the type of staging classification used (TNM or MK) overall and for the assessment of resectability were stratified by continent. Minimally invasive techniques (video-assisted thoracoscopic surgery and RATS) were less frequently used by responders from Europe ($p = 0.04$); responders from the Americas were significantly more reluctant and less likely to participate in international databases versus those from Asia and Europe ($p = 0.007$). Responders from Asia indicated a significantly higher use of TNM staging

Table 5. Perioperative Treatments (N = 217)

Question	No.	%
In your experience, how strong is the evidence to consider PORT in T1-T2-T3 (eighth edition of the UICC/AJCC TNM staging classification) completely resected thymomas?	—	—
No evidence	30	14%
Weak evidence	78	36%
Moderate evidence	64	30%
Strong evidence	22	10%
Very strong evidence	3	1%
N/A	20	9%
In your experience, how strong is the evidence to consider PORT in T1-T2-T3 (eighth edition of the UICC/AJCC TNM staging classification) completely resected thymic carcinomas?	—	—
No evidence	15	7%
Weak evidence	57	26%
Moderate evidence	57	26%
Strong evidence	48	22%
Very strong evidence	17	8%
N/A	23	10%
According to the eighth edition of the UICC/AJCC TNM staging classification of thymic tumors, do you think that PORT is indicated for the following R0 T categories THYMOMAS?	—	—
T1	19	9%
T2	65	30%
T3	149	69%
According to the eighth edition of the UICC/AJCC TNM staging classification of thymic tumors, do you think that PORT is indicated for the following R0 T categories THYMIC CARCINOMAS?	—	—
T1	72	33%
T2	128	59%
T3	170	78%
According to the eighth edition of the UICC/AJCC TNM staging classification of thymic tumors, do you think that PORT is indicated in N+ tumors?	—	—
Yes	146	67%
No	30	14%
N/A	41	19%
According to the eighth edition of the UICC/AJCC TNM staging classification of thymic tumors, for stage III tumors, do you think that preoperative chemotherapy is mandatory before operation in resectable tumors?	—	—
Yes	68	31%
No	114	53%
N/A	35	16%
According to the eighth edition of the UICC/AJCC TNM staging classification of thymic tumors, do you think that postoperative chemotherapy is necessary in the following situations:	—	—
Never	25	11%
In incomplete resections (R+)	66	30%
In N+ complete resections	89	41%
N/A	37	17%

N/A, Not applicable; PORT, postoperative radiation therapy; UICC/AJCC, Union for International Cancer Control/American Joint Committee on Cancer.

(versus MK) to assess resectability ($p = 0.0001$) than those form Europe and the Americas.

There was no significant difference among the continents with regard to the perceived importance of including capsular, mediastinal pleural, and pericardial involvements as separate T categories, and all responders felt that it would be important to create separate T categories on the basis of these factors.

Responders from Asia more frequently used the ITMIG/IASLC nodal map in their clinical practice compared with those from Europe and the Americas ($p = 0.025$); as for the intraoperative lymph nodal dissection, responders from the Americas reported significantly lower N1 and N2 lymph nodal resection rates for both thymomas and thymic carcinomas than those reported by responders from Asia and Europe ($p <$

0.05). Finally, responders from Asia reported a significantly higher lymph nodal resection rate using minimally invasive techniques than that reported by responders from Europe and the Americas ($p = 0.005$).

Discussion

The present survey by IASLC SPFC-TD indicates that the eighth edition of the UICC/AJCC TNM staging classification of thymic tumors is gaining acceptance, and it is perceived as a useful system, although the MK staging classification is still being used, often in association with the TNM system.

The history of the staging classification of epithelial thymic tumors (thymomas and thymic carcinomas) includes a number of systems[6]: most classifications are non-TNM and are based on the local invasion to the neighboring structures. Of all these classifications, the M system and later the MK system gained popularity and were most frequently adopted by most centers,[7] although they were never recognized by UICC/AJCC. The M/MK classifications are surgical-pathologic staging systems, in which stage progresses mainly owing to local invasion to the adjacent structures. Lymph node involvement is included in stage IVB, with no distinction with regard to the different nodal stations.

The previous two decades have witnessed a surge of several thymic interest groups in different countries. The largest thymic organizations to date are the ITMIG,[8] JART, ESTS, ChART, KART, and the French RYTHMIC. In 2011, ITMIG and IASLC partnered to develop a proposal of a TNM staging classification, which was incorporated in the eighth edition of the UICC/AJCC TNM staging classification of thoracic malignancies.[3] Since its official introduction, several studies comparing the TNM and M/MK thymic stage classifications have been published.[9-12]

The UICC/AJCC TNM staging classification of thymic tumors represents a major paradigm shift in the staging of thymic tumors compared with the M/MK systems. Although some general concepts have been maintained, including the emphasis of the importance of the progressive involvement of adjacent structures in stage progression, some new concepts have been introduced. Among these, the consolidation of MK stage I, II, and III (mediastinal pleural involvement) into TNM stage I; the introduction of an N descriptor based on a dedicated nodal map; and the downstaging of pericardial invasion from MK stage III to TNM stage II are some of the most consequential changes. Some of these changes, such as the collapse of MK stages I to III into TNM stage I were based on the lack of detectable survival differences in the collective IASLC database analyses.

Any move from a long-standing, well-recognized stage classification into a new system requires acceptance, digestion, and a slow change of attitude, and such a major shift would take time to be universally accepted. In addition, it raises questions on how to adjust established treatment paradigms on the basis of M/MK staging systems to the new TNM classification, such as the role of PORT, which is widely considered more important for more advanced M/MK stages compared with M/MK stage I or IIA thymomas.

For this reason, the SPFC-TD decided to launch a web-based, electronic survey to be circulated among the major thymic organizations and to the IASLC members to investigate the acceptance and compliance of the scientific community to the UICC/AJCC TNM stage classification of thymic tumors.

The overall response number of the present survey was quite good (N = 217), considering the rarity of the disease. Moreover, there was a wide participation of different countries from four continents, including Africa. The results of the survey analysis therefore represent a good snapshot of how the TNM stage classification of thymic tumors is considered around the world.

Some points that may be of interest for future clinical implications need to be addressed.

First, most responders were satisfied of how IASLC advertised the TNM staging classification in the literature, web, and social media. There has been a tremendous effort by IASLC in producing flyers, plastic cards, booklets, web pages, etc., and at least from the results of the present questionnaire, the effort has been very well-perceived and appreciated by the membership; it is conceivable that in reality, the penetration of the new system in different institutions worldwide will increase over time. Although there is a perceived usefulness and user friendliness of the TNM system of thymic tumors, the MK system is currently employed by almost 90% of the responders. Physicians frequently use the TNM and MK staging systems in conjunction to help determine the stage and resultant treatment decisions. Unfortunately, it was not possible to determine for what purpose each system was being used, that is, TNM for surgical eligibility and/or MK for PORT.

When stratified by continent, the use of the TNM and MK systems was similar among the three continents, although Asian responders indicated a significantly higher use of TNM to assess surgical resectability than European and American responders. It is conceivable that the way most responders interpret the question is how evidence supports a treatment approach for categories of patients. In this case, it is likely that most responders cited the M/MK system because most published articles use this system, and the responses should therefore not be interpreted as a measure of the "acceptance" of the eighth edition of the TNM system per se.

Table 6. Results of the Survey's Responses by Continent (Americas, Asia, and Europe)

Question	Americas N = 37	Asia N = 72	Europe N = 98	*p* value
Use of MIS (VATS/RATS)	—	—	—	—
Yes	33 (89%)	67 (93%)	84 (85%)	0.04
No	3 (8%)	2 (3%)	10 (10%)	
N/A	1	3	4	
Participation in international databases	—	—	—	—
Yes	14 (38%)	45 (62%)	59 (60%)	0.007
No	23 (62%)	27 (38%)	39 (40%)	
Current use of the eighth edition UICC/AJCC TNM staging classification	—	—	—	—
Yes	24 (65%)	44 (61%)	66 (67%)	0.15
No	12 (32%)	25 (35%)	32 (33%)	
N/A	1	3	0	
Use of the Masaoka-Koga staging classification	—	—	—	—
Yes	32 (86%)	60 (83%)	87 (88%)	
No	4 (11%)	11 (15%)	11 (12%)	0.50
N/A	1	1	0	
Which staging classification is used to assess resectability?	—	—	—	—
UICC/AJCC TNM eighth edition	10 (27%)	45 (62%)	30 (31%)	0.0001
Masaoka-Koga	22 (59%)	26 (36%)	59 (60%)	
N/A	5	1	9	
Should capsular involvement be included as a separate T category in the TNM staging?	—	—	—	—
Yes	29 (78%)	58 (80%)	75 (76%)	0.30
No	7 (19%)	9 (12%)	17 (17%)	
N/A	1	5	6	
Should mediastinal pleural involvement be included as a separate T category in the TNM staging?	—	—	—	—
Yes	25 (67%)	61 (85%)	80 (82%)	0.26
No	8 (22%)	4 (6%)	11 (11%)	
N/A	4	7	7	
Should direct pericardial involvement be included as a separate T category in the TNM staging?	—	—	—	—
Yes	36 (97%)	63 (87%)	92 (94%)	0.39
No	0	3 (4%)	2 (2%)	
N/A	1	6	4	
Use of the ITMIG thymic nodal map				
Yes	15 (40%)	41 (57%)	48 (49%)	0.025
No	9 (24%)	19 (26%)	36 (37%)	
N/A	13	12	14	
N1 node dissection	—	—	—	—
Thymoma	—	—	—	—
Yes	14 (38%)	38 (53%)	52 (53%)	0.015
No	16 (43%)	20 (28%)	34 (35%)	—
N/A	7	14	12	—
Thymic carcinoma	—	—	—	—
Yes	21 (57%)	44 (61%)	73 (74%)	—
No	10 (27%)	14 (19%)	10 (10%)	
N/A	6	14	15	0.007
N2 node dissection	—	—	—	—
Thymoma	—	—	—	—
Yes	6 (16%)	18 (25%)	20 (20%)	0.24
No	24 (65%)	38 (53%)	61 (62%)	—
N/A	7	16	17	—
Thymic carcinoma	—	—	—	—
Yes	9 (24%)	26 (36%)	50 (51%)	0.01
No	21 (57%)	33 (46%)	31 (32%)	
N/A	7	13	17	

(continued)

Table 6. Continued

Question	Americas N = 37	Asia N = 72	Europe N = 98	*p* value
Do you perform node dissection during MIS (VATS/RATS)?	–	–	–	–
Never	9 (24%)	10 (14%)	19 (19%)	0.005
N1 only	13 (35%)	18 (25%)	33 (34%)	
N1 + N2	5 (13%)	27 (37%)	14 (14%)	
N/A	10	17	32	

N/A, Not applicable; ITMIG, International Thymic Malignancies Interest Group; MIS, minimally invasive surgery; RATS, Robotic-assisted thoracic surgery; UICC/AJCC, Union for International Cancer Control/American Joint Committee on Cancer; VATS, video-assisted thoracoscopic surgery.

A section of the survey investigated the perceived utility of the T and N categories. This may have an implication in the future discussion about the new revision and in the assessment of the potential utility of the categories. Although the importance of the pericardial invasion is recognized by almost all the respondents (92%), a large percentage of them are still in favor of including capsular and mediastinal pleural involvements as separate T categories. Unfortunately, we do not have information as to why responders were in favor of retaining them, despite the lack of a clear pathologic definition of the thymic capsule and the difficulty in the identification of these structures microscopically, as emphasized by pathologists.[1,13] As a consequence, a major issue among pathologists is the need for a clear definition of the histologic criteria for mediastinal pleural invasion, how to best recognize it, and the validation of the proposed criteria both retrospectively and prospectively. The concept of a capsule in most solid organ tumors is common, and it is possible that the reply to this question reflects the habits of most surgeons/pathologists to consider it important in the staging, and this may partly explain the associated use of the M/MK system that recognizes these T categories in stage progression. In addition, the analysis of the central database used for the eighth edition of the TNM stage classification, however, did not indicate a survival difference in the presence of a capsular invasion. Only the Japanese data indicate a worse disease-free survival in case of mediastinal pleural invasion. For this reason, it was agreed that the T1 descriptor be divided into T1a and T1b according to the invasion to the mediastinal pleura.[1] The inclusion of more prospective data and a longer follow-up in the databases for the next revision may bring new elements for rediscussing this issue.

The issue of the N category in the TNM stage classification of thymic tumors was considered crucial by SPFC-TD in the preparation of the survey, and the results should certainly be of interest for future discussion. In general, the compliance to the ITMIG/IASLC thymic nodal map[14,15] was fairly good, and approximately half of the responders reported using it. The percentage is reasonable, in addition to taking into consideration that until very recently, lymph node dissection has seldom been performed after the resection of thymic tumors, and the role of lymph nodal spread has long been underestimated,[16,17] with the exception of few notable contributions from Japan.[18,19] Moreover, the responses about indications and technique of lymph node dissection are in line with the ITMIG recommendations about the sampling of N1 and N2 nodes, which remain valid until proven otherwise[13] and with recent contributions indicating that the most frequent N2 involvement in thymic tumors is the ipsilateral paratracheal zone.[20] A geographic distribution in the use of lymph node dissection was reported, and Asian responders reported the highest percentage of the use of the nodal map than European and American responders. This reflects different geographic epidemiologic characteristics of thymic tumors, as suggested by some investigators,[21,22] that remain to be elucidated.

An increasing use of PORT was reported for T1 to T3 tumors, and the percentage was almost doubled for thymic carcinomas compared with that for thymomas; this is in line with recurrence rates reported in those subsets of patients. A comparison with the ESTS thymic survey,[23] although based on the MK stage classification, indicates a similar use of PORT for stage III (69%) and a higher use of PORT for stage II (61%, which corresponds to TNM stage I) in the ESTS survey. It is important to note that the classification of T1 to T3 tumors is substantially different in MK versus TNM stages. A careful understanding of the difference between the two stage classifications is essential in avoiding misinterpretations and inappropriate indications to perioperative therapies. Caution needs to be exercised when extrapolating treatment recommendations from data based on MK staging to the new TNM staging while awaiting fresh data based on the TNM stage classification. The current literature, based on MK staging, indicates that in R0 thymic tumors, there is moderate evidence to consider PORT for invasive thymomas and a stronger evidence to consider PORT for thymic carcinomas.[24-31] Little evidence has been reported to consider PORT for encapsulated thymomas because of the very low recurrence rate (<5%). PORT was perceived to be effective in N+ tumors by two-thirds of the responders, although

actually there is remarkably little data to support the notion that PORT alone is more strongly indicated in N+ disease.

As for chemotherapy, the consensus among the responders was less evident, limited (although in only 40% of the responders) to N+ disease, irrespective of histologic diagnosis (thymoma or thymic carcinoma).

The present survey has some strengths and limitations. Among the strengths, the involvement of all major national and international thymic societies (ITMIG, ESTS, JART, ChART, KART, and RYTHMIC) with the contribution of the IASLC members, allowed us to cover four continents with a fairly balanced contribution among Europe, Asia, and the Americas. Among the limitations, which are common to any survey, there is rigidity of most questions that have a "yes/no" response. In addition, the response analysis was invariably biased toward those who replied and who might theoretically be the most expert, motivated, and competent representatives and may not represent the scientific community as a whole. A further limitation is the lack of control about the accuracy of the responses, which are basically "self-reported" data, depending on the seriousness and consciousness of the responders. Finally, we acknowledge that most responders were surgeons and that most responses were skewed toward a surgical perspective, particularly those on pathologic staging and perioperative treatments, which might certainly have benefited from a larger contribution from pathologists and radiation and medical oncologists. Moreover, the collaborative work resulting in the production of this survey emphasizes the need for thymic tumors to be addressed and discussed with multidisciplinary tumor boards, in which cooperative inputs from surgeons, radiologists, radiation and medical oncologists, and pathologists are essential to make the best collective decisions.

The value of the present survey and its implication for future research is the identification of areas of controversy and disagreement toward the new TNM staging classification of thymic tumors, which might be discussed and taken into consideration by SPFC-TD for the implementation and revision of the system for the ninth edition of the TNM classification. Although it is presently unclear how these results will be used for the next revision until the new data are collected, the results of the present survey might be a good snapshot about how to direct the analysis once new data are available.

In conclusion, the results of the present survey indicate that one year after its introduction, the eighth edition of the TNM stage classification of thymic tumors has gained a reasonable acceptance among the scientific community. The survey has captured the thought of the thoracic community that the MK stage system is useful for the assessment of resectability. Surgeons and pathologists have started incorporating the concept of lymph node dissection according to the ITMIG/IASLC nodal map during resection. Asia is the continent that gives the greatest attention to the N category. The amazing collaborative effort that has been put together by IASLC and ITMIG to produce the first recognized UICC/AJCC TNM classification of thymic tumors represents the greatest paradigm shift in the management of thymic tumors in the previous decades. The work of SPFC-TD for the next edition should take into consideration this information, and at the same time, it should encourage the accrual of as many patients as possible with a widespread geographic distribution.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.11.013.

References

1. Nicholson AG, Detterbeck FC, Marino M, et al. The IASLC/ITMIG thymic Epithelial Tumors Staging Project: proposals for the T Component for the forthcoming (8th) edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2014;9(suppl 2):S73–S80.
2. Kondo K, Van Schil P, Detterbeck FC, et al. The IASLC/ITMIG thymic Epithelial Tumors Staging Project: proposals for the N and M components for the forthcoming (8th) edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2014;9(suppl 2):S81–S87.
3. Detterbeck FC, Stratton K, Giroux D, et al. The IASLC/ITMIG thymic Epithelial Tumors Staging Project: proposal for an evidence-based stage classification system for the forthcoming (8th) edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2014;9(Suppl 2):S65–S72.
4. Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. *Cancer*. 1981;48:2485–2492.
5. Koga K, Matsuno Y, Noguchi M, et al. A review of 79 thymomas: modification of staging system and reappraisal of conventional division into invasive and noninvasive thymoma. *Pathol Int*. 1994;44:359–367.
6. Filosso PL, Ruffini E, Lausi PO, Lucchi M, Oliaro A, Detterbeck F. Historical perspectives: the evolution of

the thymic epithelial tumors staging system. *Lung Cancer*. 2014;83:126–132.
7. Masaoka A. Staging system of thymoma. *J Thorac Oncol*. 2010;5(suppl 4):S304–S312.
8. Detterbeck FC. The international thymic malignancy interest group. *J Natl Compr Canc Netw*. 2013;11:589–593.
9. Liang G, Gu Z, Li Y, et al. Members of the Chinese Alliance for Research in Thymomas. Comparison of the Masaoka-Koga staging and the International Association for the Study of Lung Cancer/the International Thymic Malignancies Interest Group proposal for the TNM staging systems based on the Chinese Alliance for Research in thymomas retrospective database. *J Thorac Dis*. 2016;8:727–737.
10. Ried M, Eicher MM, Neu R, Sziklavari Z, Hofmann HS. Evaluation of the new TNM-staging system for thymic malignancies: impact on indication and survival. *World J Surg Oncol*. 2017;15:214.
11. Fukui T, Fukumoto K, Okasaka T, et al. Clinical evaluation of a new tumour-node-metastasis staging system for thymic malignancies proposed by the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee and the International Thymic Malignancy Interest Group. *Eur J Cardio Thorac Surg*. 2016;49:574–579. Epub 2015 Nov 7.
12. Meurgey A, Girard N, C Merveilleux du Vignaux, et al. Assessment of the ITMIG Statement on the WHO Histological Classification and of the eighth TNM Staging of thymic Epithelial Tumors of a Series of 188 thymic Epithelial Tumors. *J Thorac Oncol*. 2017;12:1571–1581.
13. Detterbeck FC, Moran C, Huang J, et al. Which way is up? Policies and procedures for surgeons and pathologists regarding resection specimens of thymic malignancy. *J Thorac Oncol*. 2011;7(suppl 3):S1730–S1738.
14. Bhora FY, Chen DJ, Detterbeck FC, et al. The ITMIG/IASLC thymic epithelial tumors staging project: a proposed lymph node map for thymic epithelial tumors in the forthcoming. 8th edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2014;9(suppl 2):S88–S96.
15. Carter BW, Benveniste MF, Madan R, et al. IASLC/ITMIG staging system and lymph node map for thymic epithelial neoplasms. *Radiographics*. 2017;37:758–776.
16. Ruffini E, Filosso PL, Guerrera F, Lausi P, Lyberis P, Oliaro A. Optimal surgical approach to thymic malignancies: new trends challenging old dogmas. *Lung Cancer*. 2018;118:161–170.
17. Fang W, Wang Y, Pang L, et al. Lymph node metastasis in thymic malignancies: A Chinese multicenter prospective observational study. *J Thorac Cardiovasc Surg*. 2018;156:824.e1–833.e1.
18. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. *Ann Thorac Surg*. 2003;76:878–884.
19. Kondo K, Monden Y. Lymphogenous and hematogenous metastasis of thymic epithelial tumors. *Ann Thorac Surg*. 2003;76:1859–1864. discussion 884; discussion 1864.
20. Hwang Y, Park IK, Park S, Kim ER, Kang CH, Kim YT. Lymph node dissection in thymic malignancies: implication of the ITMIG lymph node map, TNM Stage Classification, and Recommendations. *J Thorac Oncol*. 2016;11:108–114.
21. Weis CA, Yao X, Deng Y, et al. The impact of thymoma histotype on prognosis in a worldwide database. *J Thorac Oncol*. 2015;10:367–372.
22. Fang W, Yao X, Antonicelli A, et al. Comparison of surgical approach and extent of resection for Masaoka-Koga Stage I and II thymic tumours in Europe, North America and Asia: an International Thymic Malignancy Interest Group retrospective database analysis. *Eur J Cardio Thorac Surg*. 2017;52:26–32.
23. Ruffini E, Van Raemdonck D, Detterbeck F, et al. Management of thymic tumors: a survey of current practice among members of the European Society of Thoracic Surgeons. *J Thorac Oncol*. 2011;6:614–623.
24. Girard N, Ruffini E, Marx A, Faivre-Finn C, Peters S, ESMO Guidelines Committee. Thymic epithelial tumors: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(suppl 5):v40–v55.
25. Zhou D, Deng XF, Liu QX, Zheng H, Min JX, Dai JG. The effectiveness of postoperative radiotherapy in patients with completely resected thymoma: a meta-analysis. *Ann Thorac Surg*. 2016;101:305–310.
26. Rimner A, Yao X, Huang J, et al. Postoperative radiation therapy is associated with longer overall survival in completely resected stage II and III thymoma-an analysis of the international thymic malignancies interest group retrospective database. *J Thorac Oncol*. 2016;11:1785–1792.
27. Jackson MW, Palma DA, Camidge DR, et al. The impact of postoperative radiotherapy for thymoma and thymic carcinoma. *J Thorac Oncol*. 2017;12:734–744.
28. Ahmad U, Yao X, Detterbeck F, et al. Thymic carcinoma outcomes and prognosis: results of an international analysis. *J Thorac Cardiovasc Surg*. 2015;149:95–100, 101.e1–101.e2.
29. Omasa M, Date H, Sozu T, et al. Postoperative radiotherapy is effective for thymic carcinoma but not for thymoma in stage II and III thymic epithelial tumors: the Japanese Association for Research on the Thymus Database Study. *Cancer*. 2015;121:1008–1016.
30. Ruffini E, Detterbeck F, Van Raemdonck D, et al. Thymic carcinoma: a cohort study of patients from the European society of thoracic surgeons database. *J Thorac Oncol*. 2014;9:541–548.
31. Bian D, Zhou F, Yang W, et al. Thymoma size significantly affects the survival, metastasis and effectiveness of adjuvant therapies: a population based study. *Oncotarget*. 2018;9:12273–12283.